

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference L/2FW40/MIM/19	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2008/003714	International filing date (day/month/year) 06/05/2008	(Earliest) Priority Date (day/month/year) 07/05/2007
Applicant N.V. ORGANON		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/003714

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D498/04 C07D513/04 A61K31/553 A61K31/554 A61P15/00
A61P5/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM*ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/084963 A (AKZO NOBEL NV [NL]; HERMKENS PEDRO HAROLD HAN [NL]; LUCAS HANS [NL]; D) 16 October 2003 (2003-10-16) cited in the application See claims 1-15 and the examples.	1-24

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

5 August 2008

Date of mailing of the international search report

12/08/2008

Name and mailing address of the ISA/

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Authorized officer

Menchaca, Roberto

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2008/003714

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03084963	A	16-10-2003	AU 2003224161 A1	20-10-2003
			BR 0308890 A	11-01-2005
			CA 2480940 A1	16-10-2003
			CN 1649879 A	03-08-2005
			HR 20040913 A2	31-08-2005
			IS 7452 A	16-09-2004
			JP 2005528382 T	22-09-2005
			MX PA04009709 A	13-12-2004
			NZ 535546 A	26-01-2007
			RU 2309155 C2	27-10-2007
			US 2005171087 A1	04-08-2005
			ZA 200407667 A	26-07-2006

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2008/003714

International filing date (day/month/year)
06.05.2008

Priority date (day/month/year)
07.05.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C07D498/04 C07D513/04 A61K31/553 A61K31/554 A61P15/00 A61P5/24

Applicant
N.V. ORGANON

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2008/003714

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2008/003714

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-22</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-22</u>
Industrial applicability (IA)	Yes: Claims	<u>1-22</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1 Document

Reference is made to the following document; the numbering will be adhered to in the rest of the procedure:

D1: WO 03/084963 A (2003-10-16), cited in the application

2 Rule 39 PCT

Claims 23-24 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39(1)(iv) and Rule 67(1)(iv) PCT.

For the assessment of the present claims 23-24 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first or further use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Consequently, and even if no opinion should be formulated with respect to the subject-matter of these claims 23-24 (Article 34(4)(a)(i) PCT), this authority has decided to carry out and base the search and present opinion on the alleged effects of the compounds and/or compositions.

3 Novelty

No prior art document discloses (cis)-dibenzo[b,f]pyrido[1,2-d]oxazepine-2-amine or (cis)-dibenzo[b,f]pyrido[1,2-d]thiazepine-2-amine according to formula (I), in present claim 1. The subject-matter of present independent claims 1, 15-16, 19-20 and 22, respectively disclosing the above mentioned compounds, pharmaceutical compositions thereof and their therapeutical use, is therefore novel over the prior art

in the sense of Article 33(2) PCT.

Dependent claims 2-14, 17-18 and 21 fulfill, as such, the requirements of the PCT with respect to novelty (Article 33(2) PCT).

4 Inventive step

D1 is regarded as being the closest prior art to the subject-matter of the present invention and discloses (see examples; claim 1) (cis)-dibenzo[b,f]pyrido[1,2-d]oxazepine-1-amine or (cis)-dibenzo[b,f]pyrido[1,2-d]thiazepine-1-amine, useful as modulators of the progesterone receptors.

The subject-matter of the present invention further differs from this known D1 in that the compounds useful as modulators of the progesterone receptors possess the amino substituent in position 2 of the condensed heterocyclic core. In contrast, said substituent is located in position 1 of the condensed heterocyclic core in the case of the compounds from D1.

The problem to be solved may therefore be regarded as the provision of alternative compounds acting as modulators of the progesterone receptors. The applicant solves this problem by using the (cis)-dibenzo[b,f]pyrido[1,2-d]oxazepine-2-amine or (cis)-dibenzo[b,f]pyrido[1,2-d]thiazepine-2-amine according to formula (I), as disclosed in present claim 1.

The solution proposed is regarded as obvious to a person skilled in the art for the following reasons:

- the (cis)-dibenzo[b,f]pyrido[1,2-d]oxazepine and (cis)-dibenzo[b,f]pyrido[1,2-d]thiazepine derivatives are known in the art as modulators of the progesterone receptors (see, for instance, D1).
- there is no data available on file to substantiate a possible unexpected technical effect attributable to the presence of the amino substituent attached to position 2 of the heterocyclic core instead of being attached to position 1 (as in the compounds

from D1). In the absence of said unexpected technical effect, the solution proposed is regarded as being merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. Furthermore, the compounds from D1 can bear an alkyl group in said position 2 (see examples and claim 1).

- the stated progestagenic activity but no glucocorticoid activity, which the compounds of the present invention seem to exhibit does not represent any improved technical effect with respect to the analogous compounds from D1 (i.e. the closest prior art). Furthermore, due to the closely related structures, it is believed that both groups of compounds behaves in a similar way.

The subject-matter of present claims 1-22 cannot therefore be regarded as involving an inventive step in the sense of Article 33(3) PCT.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information

For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.

Amending claims under Art. 19 PCT

Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.

Filing a demand for international preliminary examination

In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/ WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT).

If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).

Filing informal comments

After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.

End of the international phase

At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).

Relevant PCT Rules and more information

Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003